

Amendments to the Specification:

Please replace the paragraph beginning on page 1, line 5 with the following amended paragraph:

The present invention relates to a DNA microarray (DNA chip) which specifically reacts with a biochemical specimen and which is used for inspection equipment represented, for example, by a biochip to be used in order to obtain information on the structure and the function of the specimen. The biochip preferably in which has several hundreds to several ten thousands kinds of captures, especially DNA fragments or the like, for capturing the specimen, and the captures are aligned and fixed at a high density as minute spots on a base plate such as a microscopic slide glass. The present invention also relates to a method for producing the same.

Please replace the paragraph beginning on page 1, line 17 with the following amended paragraph:

The ~~method~~methods for analyzing the ~~gene structure~~structures ~~has been~~have remarkably progressed in recent years. A large number of gene structures represented by those of a human gene have been ~~clarified~~identified. The analysis of the gene structure as described above uses a DNA microarray (DNA chip) in which several hundreds to several ten thousands kinds of DNA fragments or the like are aligned and fixed as minute spots on a base plate such as a microscopic slide glass.

Please replace the paragraph beginning on page 1, line 25 with the following amended paragraph:

~~These~~The methods widely used as ~~the method~~ for forming the minute spots for the production of the DNA microarray are generally based on a system such as the QUILL system, the pin & ring system, and the spring pin system in which a sample solution is stamped onto the base plate by using a pin.

Please replace the paragraph beginning on page 2, line 3 with the following amended paragraph:

Even when any one of the foregoing methods is adopted, it is important to ~~suppress~~minimize the dispersion of the volume and the shape of each of the minute spots ~~to be low~~ so that the distance between the respective minute spots is maintained to be constant. Further, it is necessary that the capture (corresponding to the DNA fragment or the like in the case of the DNA microarray), which specifically reacts with a specimen in the minute spot formed on the base plate and which is used to obtain information on the structure and the function of the specimen, is reliably immobilized on the base plate.

Please replace the paragraph beginning on page 2, line 18 with the following amended paragraph:

In the conventional production of the biochip, when the sample containing DNA fragments or the like is dropped onto the base plate to form minute spots, or when the chip is dealt with or treated thereafter, the minute spots may be peeled off. When the DNA fragments or the like are immobilized on the base plate in the DNA microarray, several techniques are adopted, in which a functional group ~~to facilitate immobilization~~ is affixed to the DNA fragments themselves to facilitate immobilization, or the surface of the base plate is coated with a functional group layer. However, even when such a technique is adopted, the adopted technique is insufficient to avoid the peeling off of the minute spots.

Please replace the paragraph beginning on page 3, line 3 with the following amended paragraph:

Further, a technique is also adopted, in which a hydrophilic polymer or the like is dissolved in a sample containing DNA fragments or the like to reinforce the immobilization of the DNA fragment or the like onto the base plate. However, the

cost may be increased, because it is necessary to ~~perform the step to mix the sample~~ and an immobilization-reinforcing solution, and it is also necessary to use a large amount of the immobilization-reinforcing solution. Further, when such an immobilization-reinforcing solution and samples are previously mixed and supplied onto the base plate, it is necessary to consider the compatibility and the conformability ~~between one type of the immobilization-reinforcing solution and the thousands of potential samples of several thousands or more types.~~ Therefore, the The selection of the material for the immobilization-reinforcing solution has been restricted.

Please replace the paragraph beginning on page 3, line 19 with the following amended paragraph:

Further, the sample containing the immobilization-reinforcing solution has to be supplied onto the base plate in accordance with the conventional method. Therefore, a drawback arises in that only ~~the~~an immobilization-reinforcing solution, which has physical properties to be successfully supplied by the supply method, can be used.

Please replace the paragraph beginning on page 3, line 25 with the following amended paragraph:

Specifically, in the method for mechanically forming spots ~~based on the use of using a pin as a general method for producing to produce~~ the DNA microarray, the sample containing the immobilization-reinforcing solution must be a sample which adheres to the pin, because the sample is physically retained (adhered) onto the pin to move (supply) the sample onto the base plate. Further, it is necessary that the amount of adhesion is made as uniform as ~~far as possible~~ for all cases of DNA fragments or the like ~~of several thousands or more types.~~ Therefore, the selection of the immobilization-reinforcing ~~agent~~agents that can to be mixed with DNA fragments or the like has been extremely restricted.

Please replace the paragraph beginning on page 4, line 19 with the following amended paragraph:

In the non-contact type spotting method, a biological sample, which contains, for example, DNA fragments, nucleic acids, and amino acids, is discharged as minute droplets ~~to the space so that the sample is dropped onto a base plate such as a slide glass.~~

Please replace the paragraph beginning on page 4, line 24 with the following amended paragraph:

However, in this method, when the minute droplets of the biological samples, which have having relatively high viscosities, are of many different types, and differ only slightly~~which are of several hundreds to several ten thousands types with delicate differences in physical properties of the respective solutions, are discharged to the space so that the minute droplets are~~and dropped onto the slide glass base plate. Therefore, the so-called satellites (splashed droplets finer than objective discharged droplets) tend to appear ~~during the discharge~~ in addition to the objective droplets (objective discharged droplets). The satellites ~~are dropped onto the base plate, resulting~~result in problems ~~on~~of quality of the obtained product. ~~for~~ For example, such that spots are formed at portions other than original spot formation positions, ~~and making~~ it is impossible to maintain constant spacing distances between the minute spots ~~to cause any~~and causing contamination due to the mixing with each other.

Please replace the paragraph beginning on page 5, line 13 with the following amended paragraph:

The so-called satellites as described above are not caused at the early stage of the operation of the dispenser in some cases, but the satellites occur after continuing the operation for a certain period of time. An extremely troublesome problem arises in

this way in view of the management of production steps. When the discharge speed of the droplets is large, the momentum of the droplets is large upon the dropping onto the slide glass base plate, resulting in a problem such that splashes (mists) are generated to form unnecessary spots (also referred to as forming "satellites") around the genuine spot.

Please replace the paragraph beginning on page 5, line 24 with the following amended paragraph:

In order to avoid the occurrence of the so-called satellites as described above, the discharge speed may be decreased. However, if the discharge speed is decreased, the discharge operation ~~is~~becomes unstable.

Please replace the paragraph beginning on page 6, line 1 with the following amended paragraph:

When the method, in which the hydrophilic polymer or the like is dissolved in the sample containing DNA fragments or the like to reinforce the immobilization of the DNA fragments or the like onto the base plate as described above, is adopted for the ink-jet type spotting method, the sample solution is discharged onto the base plate through a discharge nozzle. However, the solidification of the sample solution may be advanced during the process ~~for~~of discharging the sample solution onto the base plate, resulting in discharge failure. ~~Especially, when~~When an immobilization solution having a high viscosity is mixed with the sample to effect the discharge, any discharge defect is likely caused by the drying and solidification of the sample solution in the vicinity of the discharge nozzle.

Please replace the paragraph beginning on page 6, line 15 with the following amended paragraph:

Further, when it is intended to actually obtain information on the structure or

the function of a specimen, the specimen is ~~nonspecifically~~ may be bound to the base plate in locations other than the spots. Conventionally, in order to avoid such a phenomenon, a blocking treatment (treatment to avoid any binding of the specimen to portions other than portions at which the spots are formed on the base plate) is performed after forming the spots on the base plate. However, most of captures supplied onto the base plate may flow out during the blocking treatment. Further, the blocking treatment may be incomplete and the S/N ratio of the signal from the spot is deteriorated.

Please replace the paragraph beginning on page 7, line 2 with the following amended paragraph:

The present invention has been made taking the foregoing problems into consideration; ~~an~~ An object of which the present invention is to provide a biochip and a method for producing the same in which a high quality biochip having a high S/N ratio ~~of a signal from a spot is successfully produced without any missing any of the~~ minute ~~spots~~ spots of a sample containing DNA fragments or the like; ~~This making makes~~ it possible to simplify the production steps, reduce the cost, and improve the yield.

Please replace the paragraph beginning on page 7, line 10 with the following amended paragraph:

According to the present invention, there is provided a biochip comprising a large number of spots based on capture solutions, the spots being arranged on a base plate by supplying, onto the base plate, a plurality of types of the capture solutions to be used to specifically react with a specimen in order to obtain information on a structure or a function of the specimen; wherein a first substance, which acts ~~on immobilization of~~ to immobilize the captures onto the base plate, is formed at least at portions at which the spots are to be formed on the base plate. The solution sample

containing the capture herein refers to a solution obtained by dissolving or dispersing the capture in a liquid, which is also referred to as "sample containing the capture solution".

Please replace the paragraph beginning on page 8, line 5 with the following amended paragraph:

The biochip according to the present invention ~~resides in a biochip~~
~~comprising~~comprises a large number of spots based on samples containing captures, the spots being arranged on a base plate by supplying, onto the base plate, a plurality of types of the samples containing the captures to be used to specifically react with a specimen in order to obtain information on a structure or a function of the specimen; wherein the first substance, which acts on the immobilization of the captures onto the base plate, is formed at least at the portions at which the spots are to be formed on the base plate, and a second substance, which inhibits the immobilization of at least the captures onto the base plate, is formed at parts other than the portions at which the spots are to be formed.

Please replace the paragraph beginning on page 8, line 19 with the following amended paragraph:

Accordingly, the shape and the arrangement ~~form~~ of the spots ~~are~~is determined by the shape of the parts at which the second substance is not formed. Therefore, for example, inconveniences, in which the arrangement spacing between the spots is dispersed and/or the spots are ~~putted~~placed close to one another, are avoided when the samples are supplied onto the base plate. If the samples cannot be supplied to prescribed positions, the samples are prevented from contacting with the base plate ~~owing to~~because of the presence of the second substance. Therefore, no contamination source is brought about thereby. Thus, ~~the~~a biochip is obtained, which is excellent in reliability, reproducibility, and quantitative performance when ~~the~~an

analysis is performed.

Please replace the paragraph beginning on page 9, line 5 with the following amended paragraph:

When the sample is supplied in accordance with the ink-jet system, splashes or mists are often generated due to the satellite phenomenon caused when the sample is discharged. Such splashes or mists are prevented from contacting with the base plate ~~owing to~~because of the presence of the second substance. Therefore, the problem of satellites, which has been caused in the ink-jet system, is successfully ~~dissolved~~eliminated.

Please replace the paragraph beginning on page 9, line 13 with the following amended paragraph:

In other words, according to the present invention, ~~the~~a high quality biochip can be obtained inexpensively.

Please replace the paragraph beginning on page 9, line 15 with the following amended paragraph:

As for the biochip constructed as described above, it is preferable that the second substance is a substance which inhibits the immobilization of the captures onto the base plate and which inhibits the contact of the specimen with the base plate. In this case, the substance, which inhibits the contact of the specimen with the base plate, has been already present at ~~the parts other than the parts at which the spots are to be formed~~its desired location, before the formation of the spots. Therefore, it is unnecessary to perform the blocking treatment for each of the spots after the formation of the spots. Accordingly, it is possible to reliably obtain a large amount of the capture to be immobilized onto the base plate as compared with an ordinary biochip. As a result, the sensitivity to the specimen is improved.

Please replace the paragraph beginning on page 10, line 7 with the following amended paragraph:

Accordingly, the shape of the parts at which the second substance that determines the shape and the arrangement form of the spots is not formed can be prescribed only by ~~only~~ the formation of the second substance. Therefore, ~~the~~ a biochip, in which the dispersions of the spacing distance between the spots and the individual shapes are suppressed, is realized. As a result, it is possible to perform an accurate analysis in which the sensitivity to the specimen is uniform.

Please replace the paragraph beginning on page 10, line 15 with the following amended paragraph:

According to another aspect of the present invention, there is provided a method for producing a biochip comprising a large number of spots based on capture solutions, the spots being arranged on a base plate by supplying, onto the base plate, a plurality of ~~types of the capture solutions~~ solution types to be used to specifically react with a specimen in order to obtain information on a structure or a function of the specimen; the method comprising the step of supplying a solution sample containing the capture and a solution sample containing no capture separately from each other to produce the biochip. In this process, it is preferable that the solution sample containing the capture is supplied in accordance with an ink-jet system.

Please replace the paragraph beginning on page 11, line 5 with the following amended paragraph:

When the sample containing the capture solution and the sample containing no capture solution are supplied separately from each other, the sample containing no capture solution can be selected only in view of the property that the sample containing no capture solution has the ~~performance~~ ability to reliably immobilize and retain the capture on the base plate, which is preferred. Further, the sample containing

the capture solution can be supplied by a supply means which is distinct from a supply means for the sample containing no capture solution. Therefore, it is possible to employ a supply method which is optimum for each of the solutions.

Please replace the paragraph beginning on page 19, line 18 with the following amended paragraph:

When the substances of the capture, the immobilization solution, and the immobilization-reinforcing solution are combined as described above, the immobilization of the capture onto the base plate is ~~more-strengthened~~. Further, when this feature is combined with the method in which the solution containing the capture and the solution containing no capture, i.e., the immobilization solution or the immobilization-reinforcing solution are supplied onto the base plate separately from each other in accordance with the basic concept of the present invention, the immobilization proceeds in a form in which the orientation is ~~uniformalized~~made uniform for the captures, i.e., the captures are spread over the base plate three-dimensionally. It is easy for the capture to capture the specimen. As a result, the quality of the biochip is improved.

Please replace the paragraph beginning on page 20, line 6 with the following amended paragraph:

Further, when the solutions are supplied separately from each other, the functions of the immobilization solution and the immobilization-reinforcing solution are prevented from ~~deterioration~~deteriorating which would be otherwise caused by any influence exerted by drying or the like brought about by being ~~left to stand in the atmospheric air~~exposed to the atmosphere. Accordingly, it is preferred that the solutions are supplied onto the base plate while retaining the original functions of the foregoing substances, ~~which is preferred~~.

Please replace the paragraph beginning on page 20, line 15 with the following amended paragraph:

Further, when the water-retentive substance is used for the immobilization-reinforcing solution, as preferred, the immobilization reaction for the capture to be immobilized on the base plate can be sufficiently advanced ~~in an enough~~ over a period of time by retaining water in the spots, ~~which is preferred~~.

Please replace the paragraph beginning on page 20, line 20 with the following amended paragraph:

Further, when the high-molecular substance is used for the immobilization-reinforcing solution, as preferred, then the capture is freely movable in the immobilization-reinforcing solution, and the immobilization or the capture of the specimen by the capture is not inhibited, ~~which is preferred~~.

Please replace the paragraph beginning on page 21, line 25 with the following amended paragraph:

Accordingly, the shape of the spot, in which each of the captures of the biochip exists, is determined by the spot shape of ~~one type of the~~ sample containing no capture solution. Therefore, it is possible to eliminate the deviation of the spot shape which would be otherwise caused by the difference in the type of the capture.

Please replace the paragraph beginning on page 23, line 13 with the following amended paragraph:

This positive effect is exerted on ~~not only more than just~~ the satellite problem. The same or equivalent effect is ~~preferably also~~ exhibited also for the "problem of so-called flight curvature resulting in dispersion of discharge direction" which possibly may be ~~possibly caused in the case of~~ with the ink-jet system.

Please replace the paragraph beginning on page 23, line 27 with the following amended paragraph:

According to still another aspect of the present invention, there a method is provided ~~a method~~ for producing a biochip comprising the steps of providing a first substance, which acts ~~on said immobilization of~~ immobilizes the captures onto said base plate; ~~at portions at which at least~~ where the spots are to be formed, and forming a second substance for inhibiting ~~at least immobilization of~~ the captures onto the base plate at parts ~~other than portions at which~~ where the spots are not to be formed ~~on the base plate provided with the first substance.~~

Please replace the paragraph beginning on page 24, line 9 with the following amended paragraph:

Accordingly, the solution containing the capture is subjected ~~to the~~ spotting ~~spotted~~ onto the base plate by using the base plate ~~on which~~ where the first substance is already formed at the portions to be subjected ~~to the spotting~~ beforehand ~~spotted~~ and the second substance is formed at the portions other than the above. The shape and the arrangement ~~form~~ of the spots are determined by the shape of the parts ~~at which~~ where the second substance is not formed. For example, inconveniences, in which the arrangement spacing between the spots is dispersed and the spots are ~~putted~~ placed close to one another, disappear. Further, when the sample cannot be supplied to the prescribed position, the sample is prevented from contacting with the base plate ~~owing to~~ because of the presence of the second substance. Therefore, no contamination source is generated. Splashes or mists, which are caused by the satellite phenomenon often caused during the discharge of the sample when the sample is supplied in accordance with the ink-jet system, are prevented from contacting with the base plate ~~owing to~~ because the presence of the second substance. Therefore, it is possible to ~~dissolve~~ eliminate the problem of ~~satellites~~ satellites having been ~~hitherto~~ caused by the ink-jet system. The present invention is advantageous as

described above. It is possible to produce the high quality biochip. It is possible to simplify the production steps, reduce the cost, and improve the yield.

Please replace the paragraph beginning on page 26, line 22 with the following amended paragraph:

When the sample is supplied in accordance with the ink-jet system, the high speed supply can be realized. However, the satellite phenomenon is often caused during the discharge of the sample, and the base plate is polluted in some cases. However, splashes or mists, which are caused by the satellite phenomenon, are prevented from contacting with the base plate owing to the presence of the second substance. Therefore, the problem of ~~satellites~~satellites, which has been ~~hitherto~~ caused in the ink-jet system, is successfully ~~dissolved~~eliminated. Therefore, the supply of the sample in accordance with the ink-jet system can be actively facilitated.

Please replace the paragraph beginning on page 36, line 12 with the following amended paragraph:

After that, the base plate 10 is taken out, ~~and it is~~ transferred into distilled water, ~~followed by being~~and is rinsed to remove the alkaline solution. Subsequently, the base plate 10 is immersed in a poly-L-lysine solution prepared by adding poly-L-lysine to distilled water, followed by being left to stand for 1 hour.

Please replace the paragraph beginning on page 41, line 8 with the following amended paragraph:

A nozzle sheet 48 is formed with the sample discharge port 54. The sample discharge port 54 is formed through a resin film ~~by means of the~~using an excimer laser machining.

Please replace the paragraph beginning on page 41, line 11 with the following amended paragraph:

The micropipette 34 constructed as described above is operated as follows. That is, when an electric field is generated between the upper electrode 74 and the lower electrode 70, ~~then the piezoelectric layer 72 is deformed, and the~~ The vibrating section 66 is then deformed in accordance therewith. Accordingly, the volume of the cavity (pressurizing chamber) 56 contacting with the vibrating section 66 is decreased.

Please replace the paragraph beginning on page 41, line 19 with the following amended paragraph:

When the volume of the cavity 56 is decreased, the sample 14 or the immobilization-reinforcing solution 16 charged in the cavity 56 is discharged at a predetermined speed from the sample discharge port 54 which communicates with the cavity 56. As shown in FIG. 3, it is possible to prepare the biochip 20 in which the sample 14 and the immobilization-reinforcing solution 16 discharged from the micropipettes 34 are aligned and fixed as minute spots 80 on the base plate 50 10 such as a microscopic slide glass.

Please replace the paragraph beginning at page 43, line 8 with the following amended paragraph:

As shown in FIG. 5A, a plurality of pins 38 for positioning and fixing the micropipettes 34 are provided on the upper surface of the fixation plate 32. When the micropipette 34 is fixed on the fixation plate 32, the micropipette 34 is placed on the fixation plate 32 while inserting the pins 38 of the fixation plate 32 into positioning holes 90 (see FIG. 5C) provided at the both sides of the substrate 50 of the micropipette 34. Thus, a plurality of micropipettes 34 are automatically positioned and aligned with a predetermined array arrangement.

Please replace the paragraph beginning on page 43, line 18 with the following amended paragraph:

Each of the fixing jigs 36 has a holder plate 100 for pressing the plurality of micropipettes 34 against the fixation plate 32. Insertion holes for inserting screws 102 thereinto are formed through both end portions of the holder plate 100 respectively. When the screws 102 are inserted into the insertion holes, and they are screwed into the fixation plate 32, then the plurality of micropipettes 34 can be pressed against the fixation plate 32 ~~by~~with the aid of the holder plate 100 ~~at one~~. One unit is constructed by the plurality of micropipettes 34, which are pressed by one holder plate 100. As shown in FIG. 5A, one unit is constructed by the five micropipettes 34 which are arranged in the direction of the column.

Please replace the paragraph beginning on page 44, line 4 with the following amended paragraph:

The holder plate 100 is formed with introducing holes 104 (see FIG. 5B) which are used to supply the samples 14 and the immobilization-reinforcing solutions 16 to the portions corresponding to the sample-pouring ports 52 of the respective micropipettes 34 ~~respectively when the plurality of micropipettes 34 are pressed.~~ Tubes 106 for introducing the samples 14 and the immobilization-reinforcing solutions 16 to the introducing holes 104 ~~respectively are held at upper end portions of~~ ~~the~~their respective introducing holes 104.

Please replace the paragraph beginning on page 44, line 13 with the following amended paragraph:

Considering the realization of the efficient wiring operation, it is preferable that the width of the holder plate 100 resides in such a dimension that the pads 76, 78 connected to ~~the~~their respective electrodes 70, 74 of the actuator section 58 are faced upwardly when the plurality of micropipettes 34 are pressed against the fixation plate

32.

Please replace the paragraph beginning on page 44, line 19 with the following amended paragraph:

As described above, the dispenser 30 ~~described above~~ is constructed such that the plurality of micropipettes 34, each having the sample-pouring port 52 and the sample discharge port 54 are provided in an upstanding manner with ~~the~~their respective sample discharge ports 54 directed downwardly.

Please replace the paragraph beginning on page 44, line 24 with the following amended paragraph:

That is, the ~~respective~~ micropipettes 34 are aligned and arranged such that ~~the~~their respective sample-pouring ports 52 are disposed on the upper side, the sample discharge ports 54 are disposed on the lower side, and ~~the~~their respective sample discharge ports 54 are aligned two-dimensionally. The samples 14 and the immobilization-reinforcing solutions 16 of mutually different types are discharged from the sample discharge ports 54 respectively.

Please replace the paragraph beginning on page 46, line 1 with the following amended paragraph:

Those piezoelectric ceramics ~~usable as the piezoelectric ceramics for the~~ piezoelectric layer 72 of the actuator section 58 include, for example, lead zirconate, lead titanate, lead magnesium niobate, lead magnesium tantalate, lead nickel niobate, lead zinc niobate, lead manganese niobate, lead antimony stannate, lead manganese tungstate, lead cobalt niobate, and barium titanate, as well as composite ceramics containing components obtained by combining any of them. However, in the embodiment of the present invention, a material containing a major component composed of lead zirconate, lead titanate, and lead magnesium niobate is preferably

used, for the following reason.

Please replace the paragraph beginning on page 46, line 19 with the following amended paragraph:

Further, in the embodiment of the present invention, it is also preferable to use ceramics obtained by appropriately adding, to the piezoelectric ceramics described above, for example, oxides of lanthanum, calcium, strontium, molybdenum, tungsten, barium, niobium, zinc, nickel, manganese, cerium, cadmium, chromium, cobalt, antimony, iron, yttrium, tantalum, lithium, bismuth, and stannum, or a combination of any of them, or ~~other-compounds~~ thereof.

Please replace the paragraph beginning on page 60, line 19 with the following amended paragraph:

Accordingly, for example, inconveniences, in which the arrangement spacing between the spots 180 is dispersed and the spots 180 are ~~putted~~placed close to one another, disappear when the samples are supplied onto the base plate 112. Further, when the sample cannot be supplied to the prescribed position, the sample is prevented from contact with the base plate 112 owing to the presence of the second substance 118. Therefore, no contamination source is generated.

Please replace the paragraph beginning at page 61, line 1 with the following amended paragraph:

Further, splashes or mists, which are caused by the satellite phenomenon often caused during the discharge of the sample when the sample is supplied in accordance with the ink-jet system, are prevented from contact with the base plate 112 owing to the presence of the second substance 118. Therefore, it is possible to ~~dissolve~~eliminate the problem of ~~satellites~~satellites having been ~~hitherto~~ caused by the ink-jet system.